a)Título:

**TESTES VISCOELÁSTICOS NA AVALIAÇÃO DE ALTERAÇÕES DA HEMOSTASE NA INFEÇÃO POR SARS-CoV2**

**VISCOELASTIC TESTS IN THE EVALUATION OF HAEMOSTASIS DISTURBANCES IN SARS-CoV2 INFECTION**

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e) Título para cabeçalho:

**VISCOELASTIC TESTS IN THE EVALUATION OF HAEMOSTASIS DISTURBANCES IN SARS-CoV2 INFECTION**

a) **TITLE**

**VISCOELASTIC TESTS IN THE EVALUATION OF HAEMOSTASIS DISTURBANCES IN SARS-CoV2 INFECTION**

b) **ABSTRACT**

A coagulopatia associada à COVID-19 é uma disfunção associada à infeção SARS-CoV2 grave, caraterizada por aumento significativo do fibrinogénio, D-dímeros e Proteína C reativa e por valores normais/muito pouco alterados do tempo de protrombina, tempo de tromboplastina parcial ativado e n.º de plaquetas. A hipercoagulabilidade e a hipofibrinólise coexistem e são detetadas por testes viscoelásticos. Quando associadas à imobilização e aos fatores de risco intrínsecos do paciente (idade, obesidade, comorbilidades, drogas), potenciam eventos tromboembólicos, apesar da tromboprofilaxia. Os pulmões são o órgão primeira e mais gravemente afetado.

Até à data, a maioria dos doentes apresentou hipercoagulabilidade nos testes viscoelasticos, não detetada pelos testes de coagulação de rotina e foi reportada uma elevada taxa de eventos trombóticos, sugerindo que esta deveria ser considerada uma das causas de deterioração clínica, não só em cuidados intensivos.

Na coagulopatia associada à COVID-19 avançada, o n.º de plaquetas e o fibrinogénio podem diminuir significativamente, dependendo da gravidade clínica da infeção, assemelhando-se o quadro a uma coagulopatia de consumo. Nesta fase pode haver hemorragia, especialmente se o paciente estiver sob *extracorporeal membrane oxygenation*.

Os testes viscoelásticos afiguram-se muito úteis para avaliar a hipercoagulabilidade e a hipofibrinólise em doentes críticos SARS-CoV2 com coagulopatia associada à COVID-19, parecendo também promissores para a gestão da anticoagulação.

No entanto, é necessária mais investigação para determinar se testes viscoelásticos alterados, *per si* ou combinados com outros resultados clínicos/laboratoriais, podem identificar os doentes com risco trombótico acrescido.

Ensaios clínicos para avaliação da hipercoagulabilidade por testes viscoelásticos e da necessidade de personalização da anticoagulação em doentes SARS-CoV2 estão a emergir rapidamente.

COVID-19 associated coagulopathy is a dysfunction of severe SARS-CoV2 infection, characterized by significantly increased fibrinogen, D-dimer and C reactive protein and normal to near-normal prothrombin time, activated partial thromboplastin time and platelet count. Hypercoagulopathy and hypofibrinolysis coexist and are detected by viscoelastic tests. These features when associated with immobilization and the intrinsic risk factors (age, obesity, comorbidities, drugs) of the patient, cause thromboembolic events, despite thromboprophylaxis. The lungs are the first and most severely damaged organ.

To date, most patients have exhibited hypercoagulability on viscoelastic tests not detected by standard coagulation tests. A high rate of thrombotic events was reported, suggesting that it should be considered as a cause of clinical deterioration in intensive care and potentially beyond.

In advanced stage COVID-19 associated coagulopathy, fibrinogen and platelet count can decrease significantly, depending on the severity of clinical status resembling consumptive coagulopathy. In this stage, bleeding events can occur, especially if the patient is under extracorporeal membrane oxygenation.

Viscoelastic tests are very useful tools to assess hypercoagulability and hypofibrinolysis (not detectable by standard coagulation tests) in critically ill SARS-CoV2 patients with COVID-19 associated coagulopathy, and look like very promising tools for anticoagulation management.

However, further research needs to be carried out to determine whether abnormal viscoelastic tests alone or in combination with other clinical or laboratory findings can identify patients at increased thrombotic risk.

Clinical trials to evaluate hypercoagulability using viscoelastic tests and the need for personalized dosage of anticoagulation in SARS-CoV2 patients are fast emerging.

c) **Keywords**: SARS-CoV2, Coagulopathy, Hypercoagulability, Thrombosis, Viscoelastic Testing

**INTRODUCTION**:

The major challenge associated with COVID-19 is severe, often fatal, interstitial pneumonia1. COVID-19 mortality burden is mainly attributable to a progressive bilateral pneumonia that can progress to acute respiratory distress syndrome (ARDS), requiring intensive care support2. While the pulmonary pathophysiology is not fully understood, severe COVID-19 infection is associated with an alveolar inflammatory cell infiltrate, and a systemic cytokine storm1. Proinflammatory cytokines are modulators of coagulation and fibrinolysis activation and might constitute another trigger to explain the procoagulant imbalance in these patients3. Endothelial injury may play an additional role3. *Post-mortem* studies corroborate that explanation, highlighting marked pathological changes involving lung microvasculature, disseminated micro-thrombi and haemorrhagic necrosis4. Severe COVID-19 is also associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE)2.

Several studies reported a COVID-19 associated coagulopathy (CAC)5,6, which is one of the most significant poor prognostic features7. CAC is characterized by significantly increased fibrinogen, D-dimer and C reactive protein (CRP) and normal to near-normal prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count. Hypercoagulopathy and hypofibrinolysis coexist and are more easily detected by viscoelastic tests (VET), as conventional coagulation and fibrinolytic tests only reflect parts of the coagulation2,8.

VET are *in vitro* point of care (POC) devices, capable of assessing viscoelastic properties of clotting native whole blood upon activation of hemostasis by added triggers1. This technology provides a fast and dynamic assessment of haemostasis, and it is a validated device for clinicians to make early diagnosis of the coagulopathy and to choose the most appropriate targeted treatment2. VET also measure hypercoagulability in various clinical scenarios which is not detected by standard coagulation tests (SCT)9. Global hemostatic tests such as tromboelastography and thromboelastometry are more reliable in the early identification of a hypercoagulable state (HS) and management of thrombotic scenarios in COVID-19 infection but these are not commonly used yet10. We may consider using one of the VET as a screening tool or to optimize anticoagulation therapy, particularly in acute intensive care units (ICU), although this requires further research11.

**OBJECTIVE:**

To review all relevant scientific data on the use of VET in detecting the hypercoagulability profile of SARS-CoV2 infection and its possible role in personalizing antithrombotic therapy.

**MATERIAL AND METHODS:**

A bibliographic research was performed on PubMed, Medline, Google Scholar, Cochrane and Research Gate using the conjugated keywords: “SARS-CoV2”, “COVID-19”, “Coagulopathy”, “Hypercoagulability”, “Hypercoagulable”, “Thrombosis”, “Viscoelastic Testing”, “Thromboelastometry”, “Thromboelastography”, ”SEER Sonorheometry”, “ROTEM®”,“TEG®”, “QUANTRA®”.

**RESULTS- Viscoelastic Testing**:

This review will address two similar technologies, Thromboelastography (TEG®) and Thromboelastometry (ROTEM®), and Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry (Quantra®).

TEG® and ROTEM® are both established POC VET with a wide range of applications in several scenarios4,12,13. Both devices measure coagulation in whole blood under static low shear stress conditions, without blood vessels or flow contribution14,15. When a clot starts to form inside the cup, it generates a graphically transduced signal14-16. The magnitude of displacement is termed as “clot amplitude or firmness” and relates to the strength of the clot14. The viscoelastic changes that occur during coagulation are recorded, providing a graphical representation of the fibrin polymerization13,17. This process depends on platelets, fibrinogen, and the presence of pro and anticoagulants13,17.

These devices showed a good correlation with the assessment of coagulation factors, fibrinogen and platelet count in critically ill patients18. Goal-directed transfusion therapy using this technology in different bleeding settings (trauma, perioperative and post-partum hemorrhage) are now fully studied and applied with success12,17,19. This technology has been usefully applied to areas where conventional testing is inadequate, such as hypercoagulability screening, assessment of thrombotic risk17,19,20 and the effects of systemic anticoagulants19. Its implementation requires adequate technical and interpretation training, and interdisciplinary cooperation12.

All VET parameters are shown in table 1 and ROTEM® assays and parameters in table 2. ROTEM® and TEG® parameters are comparable but not interchangeable21 (Table 1).

Use of thromboelastometry and thromboelastography in detection of HS has been described in several clinical conditions10. A short clotting time (CT) or reaction time (R-time) has been associated with a prothrombotic state19,22. The “thickness” of the VET tracing [maximum amplitude (MA) on TEG® or maximum clot firmness (MCF)/amplitude at ten minutes (A10)- INTEM or FIBTEM on ROTEM®] appears to be the most useful in guiding transfusion and predicting thrombotic complications19,20. However, no definitive definition of HS based on VET has been established.

It is recommended by the Chinese experts’ consensus18, and other authors23, to use VET to evaluate severe CAC and monitor anticoagulation therapy in critically ill patients.

Direct thrombin inhibitors (DTI) (Argatroban, Bivalirrubin) are used in COVID-19 infected patients with significantly lower antithrombin levels24, or if heparin induced thrombocytopenia (HIT) occurs. DTI inhibit thrombin in the Clauss reagent, underestimating fibrinogen quantification, making VET a valid method for monitoring fibrinogen levels in this setting.24

Emerging studies using VET aim to address the hemostatic changes found in SARS-CoV2 infection, but no prospective randomized clinical trial (RCT) data is available13.

**ROTEM®** (Rotational Thromboelastometry)

***Overview:***

ROTEM® delta is a semi-automated system that provides four independent channels12. The ROTEM® sigma is a cartridge-based fully-automated closed system, including four assays12 (Tables 1,2; Figure1).

Thromboelastometry has been proven useful in identifying hypercoagulability in various clinical settings not detected by SCT25, through the presence of (a) an accelerated clot formation with significantly lower clot formation time (decreased CFT-EXTEM/INTEM/FIBTEM) due to the increase of plasma fibrinogen and excessive thrombin generation, and/or (b) an increase in clot strength (increased MCF-EXTEM/INTEM/FIBTEM and A10) and higher α angle2,25-27. INTEM clot firmness at 10 minutes (A10) was the best predictor of thromboembolic complications26. MCF is a reliable marker of hypercoagulability27. CT, CFT, and α angle are valuable to estimate thrombin generation28.

A *Hypercoagulability profile* is defined by ROTEM® analysis as12,29: CT-EXTEM: <40s-<45s; CFT-EXTEM: <45s-<50s; MCF-EXTEM: >68mm; MCF-FIBTEM: >22mm->24mm; LI60-EXTEM: ≤3%.

***Clinical Trials:*** (Table 3)

Theoretically, thromboelastometry variables may be affected early during the course of SARS-CoV2 infection compared with D-dimers and may be of great value as a predictor of disease severity2,27,30,31.

ROTEM® is the most used device to assess CAC. Initially, two clinical cases32,33 with severe COVID-19 ARDS requiring mechanical ventilation (MV) were described. Both revealed normal PT and APTT, very increased D-dimer and fibrinogen levels, and a HS on ROTEM® (increased MCF-EXTEM/INTEM/FIBTEM32,33, elevated α angle-EXTEM33, and decreased CFT-EXTEM32/CFT-FIBTEM33), the reason why a higher dose of unfractionated heparin (UFH) was started32,33. No thromboembolic (TE) or hemorrhagic events (HE) were observed and D-dimers have decreased32. The authors suggested that VET may have a role in rapidly identifying severe COVID-19 critically ill patients with hypercoagulability32, not detected with SCT33, and that robust anticoagulation might be needed to prevent TE32,33.

A ***Spieza et al***30 study including 22 patients admitted to the ICU, has shown evidence of hypercoagulability on ROTEM® with a shorter CFT and high clot firmness (MCF)11,30. Compared with healthy controls, the following results were observed30: (a) significantly higher fibrinogen and D-dimer levels (p<0,0001); (b) markedly hypercoagulability on ROTEM®: shorter CFT-INTEM (p=0,0002) and CFT-EXTEM (p=0,01), and higher MCF in INTEM/EXTEM/FIBTEM (P<0,001). Authors concluded that COVID-19 patients with ARF presented a severe HS rather than consumptive coagulopathy (CC). Unfortunately, this data did not allow for the assessment of the impact of adequate dosages of anticoagulants on clotting parameters11.

From ***Madathil et al***34, systemic fibrinolysis (SF) was not detected on EXTEM or FIBTEM (maximum lysis-ML: 0%) in 11 critically-ill COVID-19 patients receiving MV, despite increased CRP and D-dimer levels. Circulating plasminogen activator inhibitor-1 (PAI-1) was increased and SF is thus unlikely to occur in COVID-19 with cytokine storm. Very high D-dimers along with high CRP levels and A10-FIBTEM were observed, especially in the subset of patients with very high D-dimer (>3245ng/ml), but without elevated ML-EXTEM (0%), suggesting that SF is unlikely to occur. They propose that critically-ill COVID-19 patients demonstrated significant elevations in D-dimer levels consistent with microvascular thrombosis, but only small fractions of fibrin seem to be locally broken down34.

*Fibrinolysis shutdown* was evidenced in others studies14,27,35 by raised D-dimer and complete failure of clot lysis at 30 minutes on thromboelastography (LY30) and thromboelastometry (LI30), which predicts and correlates with TE and the need for hemodialysis in critically-ill COVID-19 patients14,35. Authors hypothesize that the main source for elevated levels of D-dimers in the presence of hypercoagulability, plus decreased fibrinolysis, could be the lungs35.

Another study36 conducted in 78 COVID-19 patients (48 with ARDS in ICU; 30 in ward), despite substantial heparin plasma levels (mean anti-Xa activity of 0.35±0.20IU/ml) and normal levels of antithrombin in 91% of patients, thrombin generation was normal. These findings plus significantly increased fibrinogen and FVIII, suggested high risk hypercoagulability, probably related to major inflammatory syndrome, not controlled by heparin36. A TEM-tPA assay was used to detect both hypercoagulability and hypofibrinolysis simultaneously, and is a promising biomarker of thrombosis risk36.

***Pavoni et al***2 study included 40 critically-ill COVID-19 patients where SCT and ROTEM® were evaluated on ICU admission day (T0) day 5 (T5) and 10 (T10). On ICU admission, PT was slightly reduced, and increased significantly at T10 (p=0.002), while APTT and fibrinogen values were higher at T0 than T10 (p=0.017; p=0.002, respectively). Platelet count was normal and increased over time. 70% of patients had higher D-dimer levels that decreased at T10 (p=0.392). ROTEM® profiles were consistent with hypercoagulability (lower CFT, increased MCF) which persisted in the first five days, decreasing after ten days, without returning to normal values2. No sign of secondary hyperfibrinolysis or sepsis-induced coagulopathy were found2. 15% and 30% of patients had DVT and catheter-related thrombosis respectively, despite low molecular weight heparin (LMWH) prophylaxis2. In conclusion, ROTEM® showed consistent evidence of a HS in severe COVID-19 that persisted over time associated with an inflammatory state, rather than CC2. The improvement of fibrinogen clot firmness measurements after 10 days of illness suggests a dynamic component for the changes in coagulation that accompany the rise and fall of inflammatory parameters37.

***Almskog et al***27, evaluated whether patients with severe disease have a more pronounced hypercoagulability compared with less severely ill COVID19 patients, using ROTEM® analysis. They included 60 COVID-19 patients divided into two groups depending on care level (regular wards and ICU) and were compared with 89 healthy controls. SCT and ROTEM® analysis were performed as soon as possible after admission. 80% of patients received prophylaxis with LMWH. Near normal levels of INR, APTT, and platelets, although markedly elevated D-dimer and fibrinogen levels were observed. There was no significant correlation between D-dimer and MCF-EXTEM (p=0.9), but it was significant between fibrinogen and MCF-FIBTEM (p<0,001)27. When compared with healthy controls, COVID-19 patients ROTEM® variables were significantly higher in both groups (ward/ICU) (p<0,0001), and were higher in the severely ill compared with the less ill on regular wards (p<0,01 for MCF-EXTEM and p<0,05 for FIBTEM); CT-EXTEM was significantly longer, particularly in ICU patients (p<0,001), and CFT-EXTEM significantly shorter in COVID-19 (p<0,001)27. All these ROTEM® variables determined early after admission were significantly more pronounced in patients with increased severity27. This suggested prolonged hemostatic initiation, shortened clot propagation, and pronounced clot firmness, indicating hypercoagulability27. The authors concluded that hypercoagulability is present in hospitalized patients at an early disease course with mild to severe COVID-19 pneumonia and ROTEM® analysis may be a potentially useful predictor of TE and mortality27.

Two prospective studies38,39 demonstrated that most patients admitted to ICU with severe SARS-CoV2 infection showed a pronounced HS, characterized by increased fibrinogen and D-dimer levels, impaired endogenous anticoagulation (decreased protein S levels), decreased fibrinolysis, and increased MCF-INTEM/EXTEM/FIBTEM. TE occurred in 20%38 and 33%39 of patients despite appropriate anticoagulation, and HE in 10%38. The magnitude of coagulation abnormalities seemed to correlate with the severity of organ dysfunction according to the sequential organ failure assessment (SOFA) score being higher if SOFA>1038. Compared with SOFA≤10, COVID-19 patients with SOFA>10 exhibited higher fibrinogen and D-dimer levels, higher MCF-FIBTEM (p=0.05), lower ML-INTEM (p=0.004), and lower antithrombin, protein C and plasminogen levels38.

**TEG®** (Thromboelastography)

***Overview:***

Thromboelastography parameters include reaction time (R, represents the initiation phase measuring the time from the start of the test to initial fibrin formation), clot formation time (K, represents amplification phase measuring the time until 20mm of clot strength is achieved), angle or α (K angle, represents the propagation phase measuring the rate of clot formation), maximum amplitude (MA, represents the overall stability of the clot), and amplitude at 30 minutes (LY30, represents the fibrinolysis phase and measures the percentage of decrease in amplitude at 30 minutes post-MA)37. The new TEG®6s system is fully automated21.

In TEG® (Table 1, Figure 1), hypercoagulability is shown by shorter R-time and K-time, besides increased K/α angle and MA17,22,40. Hypercoagulability in the *Mazen et al* study22 was defined by having at least three abnormal TEG® values. However, *Maatman et al*40, defined a hypercoagulable profile as two or more thromboelastographic parameters beyond one SD of the age-and gender-matched controls.

***Clinical Trials*** (Table 3)

***Panigada et al***1 showed hypercoagulability together with a severe inflammatory state based on SCT and thromboelastography testing on severe SARS-CoV2 infection. Escalating the LMWH dose from prophylactic to therapeutic requires a careful approach based on the benefit/risk ratio until clinical trials are available1.

Similar results were observed by ***Maatman et al***40 and ***Wright et al***41, showing COVID-19-associated hypercoagulability and fibrinolysis shutdown (LY30<0.8%) both measured by TEG®41 in 12 and 44 patients admitted to the ICU, respectively40,41causing a higher rate of VTE40.

Similarly, ***Mortus et al***42 found high K/α angle or high MA on TEG® in 90.5% of patients with severe COVID-19, including increased fibrinogen activity (>73o angle) plus MA (>65mm) in 74% of patients, and MA criteria alone in 26%. TE occurred at a 62% rate despite thromboprophylaxis in all. In comparison, innate TEG®-MA was significantly greater for the high TE rate group than the low TE rate group (p=0.01)42. Increased MA was observed in 100% and 45% of patients in the high and low event rate group respectively. Hypercoagulable innate TEG®-MA yieldoseed 100% sensitivity and 100% negative predictive value for the occurrence of multiple thrombs42. In conclusion, in this context, TEG® may be critical in identifying patients at increased thrombotic risk, where full heparinization is beneficial, and avoiding unnecessary anticoagulation in those with low thrombosis risk42.

According to ***Fan et al`s*** findings10, TEG® appears to be a useful tool in detecting hypercoagulability even in the presence of heparin or antiphospholipid syndrome in CAC.

**QUANTRA®** (SEER Sonorheometry)

***Overview:***

Quantra® is a new fully automated VET closed system POC16,43, that allows rapid whole blood global hemostasis evaluation within 15 minutes of test initiation, using self-contained cartridges43 (Table 1, Figure 1).

Quantra® uses ultrasound technology14,16 for direct measurement of physical properties of the clot, without mechanical clot disruption14,43. The ultrasound pulses generate a shear wave in the sample and the resulting deformation is measured16. The frequency and amplitude of the induced deformation are directly related to the sample’s viscoelastic properties16.

The following functional parameters can be analyzed14,16,43 (Table 1): clot time (CT) after blood activation with kaolin44, provides an indication of the functional status of coagulation factors that lead to fibrin formation43; CT with Heparinase I to neutralize heparin (CTH); CT Ratio (CTR) (CTR>1,4 indicates the likelihood of heparin`s influence); clot stiffness (CS), measured 7 minutes after clot initiation, provides information about fibrin/fibrinogen function and platelet activity in the presence of thromboplastin, and was compared with A10-EXTEM on ROTEM®16. It represents the platelet-fibrinogen interaction through thrombin and factor XIII, but is also influenced by hematocrit and acidosis14; fibrinogen contribution to CS (FCS) reflects only fibrinogen’s contribution to the overall CS (hPa)16,43, being compared with A10-FIBTEM on ROTEM®16; platelet contribution to CS (PCS), and also platelet activation and platelet contraction of the fibrin mesh15,16,43, is a parameter calculated by taking into account the difference between CS and FCS15,16,43; and clot stability to lysis (CSL).

Quantra® enables a goal-directed therapy for bleeding patients in several clinical settings43, as well as diagnosis and evaluation of hypercoagulability as seen in COVID-19. Quantra® has a good correlation with other well-established VET devices and the Clauss assay14,16,43.

***Clinical Trials:*** (Table 3)

Several publications concerning COVID-19 patients have demonstrated a procoagulant profile with increased clot strength, platelet and fibrinogen contribution to clot stiffness (PCS,FCS) 11,44, which seemed to improve during ICU stay under anticoagulation11,44,45. Besides, CT and CTH parameters can be useful to monitor anticoagulation.

***Ranucci et al`s***44 study aimed to characterize the coagulation profile of COVID-19 ARDS patients, and to evaluate their changes after aggressive thromboprophylaxis. The 16 patients received a complete coagulation profile at ICU admission, as well as MV. Ten patients were monitored in the subsequent 7 days, after increased LMWH dose, antithrombin corrected if <70%, and clopidogrel if platelet count >400x109/L44. Major TE were not observed. At baseline, procoagulant profile was characterized by normal values of CT, but elevation of CS, PCS, FCS, D-dimer, and fibrinogen levels, which were associated and correlated with increased interleukin-6 values (R2=0.506;p=0.003)44, confirming the link between inflammation and hypercoagulability11. After increasing thromboprophylaxis, and 2 weeks from the baseline, there was significant time-related decrease of fibrinogen levels (p=0.001), D-dimers (p=0.017), CS (p=0.013), PCS (p=0.035), and FCS (p=0.038)44.

***Masi et al***45 characterized the coagulation and fibrinolysis profiles of 17 COVID-19-associated ARDS patients and compared them with 11 non-COVID-19-associated ARDS patients. On admission, all received thromboprophylaxis. PE was incidentally diagnosed in 17% of patients45. Compared to non-COVID-19, COVID-19 patients exhibited: (a) significantly higher levels of procoagulant factors, mainly: fibrinogen (p=0.03); FV (p<0.0001); FVIII (p=0.03), and acute phase reactants45. All these parameters were strongly correlated with each other (p<0.05); (b) significantly lower thrombin-antithrombin complex (p=0.03); (c) significantly higher (p=0.048) t-PA and PAI-1, being closely correlated (p<0.001); (d) fibrinolysis shutdown or CC were not observed; (e) Quantra®, exhibited twice higher values of CS (p=0.0077), PCS (p=0.014), and FCS (p<0.001)45. CS was strongly correlated with fibrinogen (p=0.02), FV (p=0.043), FVIII (p<0.001), but not with PAI-1 levels (p=0.606)45. In conclusion, COVID-19-associated ARDS was correlated with significant increase in procoagulants, supporting the concept of thromboinflammation45.

**DISCUSSION:**

It is crucial to be familiar with the spectrum of CAC11 since all current studies support CAC as a hypercoagulable and hypofibrinolytic state in the ICU setting37. Nevertheless, whether this hypercoagulability is due to the invading microorganism, individual viral load or the massive host inflammatory response, still remains unknown27. This hypercoagulability can evolve into CC, microthrombosis and multiple organ failure46. *Post-mortem* data supports hypercoagulability through the presence of micro-thrombi in several systems4. Activation of coagulation and/or fibrinolysis occurs in COVID-19 as part of the acute inflammatory response4. CAC may, in some way, be specific to SARS-CoV2, representing new features that need further research27.

All the observational clinical studies described point to the use of VET to assess hypercoagulability and hypofibrinolysis (not detected by SCT), and probably also for anticoagulation monitoring1,2,10,27,32,33,35,38-42. Improvements on VET parameters and patients´ clinical status were observed after introduction of tailored thromboprophylaxis1,2,30,32,44. The use of TEG® or ROTEM® is recommended by some authors18 and advised by others2,4,10,23,27,32,38 for all COVID-19 patients with severe pneumonia and coagulation dysfunction.

Hypercoagulable viscoelastic profiles1,20 were identified in several clinical studies in COVID-19 patients: increased A10, MCF (INTEM/EXTEM/FIBTEM) and α angle and decreased CFT and ML for ROTEM®2,27,30,32,35,36,38,39,46; short R, K or LYS-30 and high α angle or MA for TEG®1,11,40,42; elevated CS, PCS and FCS for Quantra®44,45.

Quantra® and ROTEM® have shown features of hypercoagulability in COVID-19 patients hinting towards their use in tailoring treatment, but these non-randomized small studies need confirmation1,20,44. The development of prospective trials prior to their use in COVID-19 patient care is strongly recommended13.

All intubated ICU patients with low bleeding risk should receive low-intensity prophylaxis with LMWH or UFH37. However, due to the very high incidence of thromboembolic complications despite standard low-dose thromboprophylaxis among severe COVID-19 patients with elevated D-dimer levels, intermediate-intensity or full-dose anticoagulation is now routinely administered37. VET have already been included in some algorithms to determine anticoagulation needs in COVID-19 ICU patients, although VET have not yet been validated as appropriate to manage anticoagulation13.

Lower 28-day mortality rate in COVID-19 patients receiving anticoagulation with LMWH was demonstrated47. Recently, the International Society of Thrombosis and Hemostasis stressed the need for implementing anticoagulation48. The latest recommendations suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic anticoagulation if such a prior indication exists18,49 or depending on patients´ weight and related risk factors49. Other strategies could include the use of intravenous UFH or DTI44 if HIT occurs18,24.

Currently, data on the utility of VET devices in CAC is still limited50. Further research is needed to investigate whether ROTEM®/TEG® are useful in identifying COVID-19 patients who might benefit from therapeutic anticoagulation, in order to guide hemostatic therapy33,35-37,50, and to determine whether an abnormal VET alone or in combination with other findings can identify a group of patients with increased thrombotic risk17,19,37.

**CONCLUSION:**

Studies concerning the use of VET to evaluate hypercoagulability on SARS-CoV2 patients are emerging.

Prospective clinical trials, ideally RCT, could underline the additional value of VET in predicting the clinical course, guidance of anticoagulation, and the risk stratification of COVID-19 patients for CAC20,47,48.

Clinical trials in hospitalized COVID-19 patients are actually underway, such as *Rotterdam cohort study using ROTEM*® (ROHOCO trial)50 and *the evaluation of hemostasis by TEG*®*, platelet function testing, and biomarker analysis* (TARGET-COVID Study37 – ClinicalTrials.gov: NCT04493307).

VET have been demonstrated to be a valuable tool to assess hypercoagulability and hypofibrinolysis in critically ill COVID-19 patients with CAC, as well as an additional contributory tool in anticoagulation management of these patients18,27. However, further research needs to be carried out in order to issue reasoned guidelines.

**CONFLICT OF INTEREST:**

The authors have disclosed no conflicts of interest.

**REFERENCES**

1. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangku V. et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A report of thromboelastography findings and other parameters of hemostasis. J. Thromb. Haemost. 2020;18(7):1738-1742. doi:10.1111/jth.14850
2. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J. Thromb. Thrombolysis 2020; 50:281-286. http://doi.org/10.1007/s11239-020-02130-7
3. Vazquez-Garza E, Jerjes-Sanchez C, Navarrete A, Joya-Harrison J, Rodriguez D. Venous thromboembolism: thrombosis, inflammation, and immunothrombosis for clinicians. J Thromb Thrombolysis. 2017;44(3):377-385. doi:10.1007/s11239-017-1528-7
4. Rubulotta F, Soliman-Aboumarie H, Filbey K, Geldner G, Kuck K, Ganau M, Hemmerling TM. Technologies to optimize the care of severe COVID-19 patients for healthcare providers challenged by limited resouces. Anesth. Analg. 2020 Aug.; 131(2):351-364. DOI:10.1213/ANE.0000000000004985
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Feb 19; 18:844-847. Doi: 10.1111/jth.14768
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z.et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11;395:1054-1062. Doi: 10.1016/S0140-6736(20)30566-3
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou C, He J. et al. China Medical Treatment Expert Group for COVID-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720. Doi: [10.1056/NEJMoa2002032](https://www.nejm.org/doi/10.1056/NEJMoa2002032)
8. Brummel KE, Paradis SG, Butenas S, Mann KG. Thrombin functions during tissue factor-induced blood coagulation. Blood. 2002;100(1):148-152. doi:10.1182/blood.v100.1.148
9. Akay OM. The Double Hazard of Bleeding and Thrombosis in Hemostasis From a Clinical Point of View: A Global Assessment by Rotational Thromboelastometry (ROTEM). Clin Appl Thromb Hemost. 2018;24(6):850-858. doi:10.1177/1076029618772336
10. Fan BE, Chia YW, Sum C, Kuperan P, Chan, S., Ling, L. M., et al. Global haemostatic tests in rapid diagnosis and management of COVID-19 associated coagulopathy in acute limb ischaemia. Journal of thrombosis and thrombolysis 2020;50(2),292–297. <https://doi.org/10.1007/s11239-020-02165-w>
11. Thachil J, Agarwal S. Understanding the COVID-19 coagulopathy spectrum. Anesthesia 2020 May 15:1-5 (Editorial). Doi:10.1111/anae.15141
12. Gorlinger K, Pérez-Ferrer A, Dirkmann D, Saner F, Maegele M, Pérez Calatayud AA et al. The Role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. Korean J. Anesthesiol. 2019 August; 72(4):297-322. doi: [10.4097/kja.19169](https://dx.doi.org/10.4097%2Fkja.19169)
13. Volod O, Reyes Gill M, Selby R, Kreiziger BL, Lee A. COVID-19 and viscoelastic hemostasis assays: frequently asked questions. Version 1.0: last updated May 11 2020. ASH online.
14. Sniecinski R, Tanaka KA. SEER Sonorheometry: Listening to what the clot has to say. Anesth. Analg. 2016;123(6):1346-1347. doi: 10.1213/ANE.0000000000001587
15. Solomon C, Ranucci M, Hochleitner G, Schochl H, Schlimp CJ. Assessing the Methodology for Calculating Platelet Contribution To Clot Stregth (Platelet Component) in Thromboelastometry and Thromboelastography. Anesth. Analg. 2015. Vol.121,nº4:868-78. DOI:10.1213/ANE.0000000000000859
16. Huffmyer JL, Fernandez LG, Haghighian C, Terkawi AS, Groves DS. Comparison of SEER Sonorheometry with rotational Thromboelastometry and Laboratory Parameters in Cardiac Surgery. Anesth.Analg. 2016; vol. 123, nº6: 1390-9. DOI:10.1213/ANE.0000000000001507
17. Luddington RJ.Thromboelastography/Thromboelastometry. Clin. Lab. Haem. 2005, 27: 81-90. <https://doi.org/10.1111/j.1365-2257.2005.00681.x>
18. Song J-C, Wang G, Zhang W, Zhang Y, Li W-Q, Zhou Z, People`s Liberation Army Professional Committee of Critical care Medicine, Chinese Society on Thrombosis and Haemostasis. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Military Medical Research 2020;7;19:1-10. <https://doi.org/10.1186/s40779-020-00247-7>
19. Harahsheh Y, Ho KM. Viscoelastic point-of-care testing to guide Transfusion and antithrombotic Therapy in perioperative and critically ill patients: are all parameters created equal?. Anaesth. Intensive Care 2016, 44:1. (Editorial). https://doi.org/10.1177%2F0310057X1604400103
20. Thachil J, Cushman M, Srivastava A. *A Proposal for Staging COVID‐19 Coagulopathy*, Res. Pract. Thromb. Haemost., 2020 May 11; 4:731–736. Doi:10.1002/rth2.12372
21. Sahli SD, Rossler J, Tscholl DW, Studt J-D, Spahn DR, Kaserer A. Point-of-Care Diagnostics in Coagulation Management. Sensors 2020; 20(15),4254:1-21. Doi:10.3390/s20154254
22. Toukh M, Siemens DR, Black A, Robb S, Leveridge M, Graham CH, et al. Thromboelastography identifies hypercoagulability and predicts thromboembolic complications in patients with prostate cancer. Thrombosis Research 2014, 133:88-95. <https://dx.doi.org/10.1016/j.thromres.2013.10.007>.
23. Allione A, Giamello JD, Paglietta G, Bernardi S, Cavalot G. Switch from oral anticoagulants to parenteral heparin in SARS-CoV2 hospitalized parents: comment. Intern. Emerg. Med. 2020, Published online: May 21:1-2. DOI:https://doi.org/10.1007/s11739-020-02373-5
24. Maier CL, Barker NA, Sniecinski R. Falsely low fibrinogen levels in COVID-19 patients on direct thrombin inhibitors. Anesth. Analg. 2020;131(2):e117-e119. DOI: 10.1213/ANE.0000000000004949
25. Akay OM. The double hazard of bleeding and thrombosis in hemostasis from a clinical point of view: a global assessment by rotational thromboelastometry (ROTEM). Clinical and Applied Thrombosis/Hemostasis 2018; vol.24(6):850-858. https://doi.org/10.1177%2F1076029618772336
26. Hincker A, Feit J, Sladen RN, Wagener G. Rotation Thromboelastometry predicts thromboembolic complications after major non-cardiac surgery, Critical Care 2014, 18:549. Doi;10.1186/s13054-014-0549-2
27. Almskog L, Wikman A, Svensson J, Wanecek M, Bottai M, Van der Linden J. et al. Rotational thromboelastometry predicts care level in COVID-19. medRxiv BMJ Yale 2020 June 23 [Ahead of print ] doi: <https://doi.org/10.1101/2020.06.11.20128710>
28. Gorlinger K, Dirkmann D, Solomon C, Hanke AA. Fast interpretation of thromboelastometry in non-cardiac surgery: reliability in patients with hypo-, normo-, and hypercoagulability. Br. J. Anaesthesia 2013, 110(2):222-30. doi:10.1093/bja/aes374
29. Gorlinger K, Pérez-Ferrer A. Algoritmos basados en test POC para el manejo de la hemorragia aguda. In Medicina Transfusional. Patient Blood management. 2ª edición. Edit. A. Pérez-ferrer, J.A.Garcia-Erce. M.Muñoz Gómez. Editorial Medica Panamericana, Espanha, Madrid, 2019, cap.9:75-110. (ISBN: 9788491102748).
30. Spieza L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campeloo E. et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiaratory failure. Thromb. Haemost. 2020; 120:998-1000. DOI: <https://doi:org/10.1055/s-0040-1710018>.
31. Juffermans N. Diagnosis and management of thrombosis in critically ill patients with COVID-19. Oral communication on Laboratory of Experimental Intensive Care and Anesthesiology (LEICA) of the Amsterdam Universitair Medische Centra (UMC) and department of Intensive Care medicine, OLVG Hospital. Online on 2020 April 19.
32. Raval Jay S, Burnett AE, Rollins-Raval MA, Griggs JR, RosenbaumE, Nielsen ND, et al. Viscoelastic testing in COVID-19: A possible screening tool for severe disease?. Transfusion 2020;60:1131-1132. Doi:10.1111/trf.15847
33. Iwasaki Y, Shiga T, Konno D, Saito K, Aoyagi T, Oshima K, et al. Screening of COVID-19 associated hypercoagulability using Rotational Thromboelastometry. J. Clin. Anesth. 2020;67:1-4. <https://doi.org/10.1016/j.jclinane.2020.109976>
34. Madathil R, Tabatabai A, Rabin J, Menne AR, Henderson R, Mazzeffi M, et al.Thromboelastometry and D-dimer elevation in Coronavirus-2019 (COVID-19). J. Cardiothoracic Vasc. Anesth. 2020 May 21: 1-2 [Ahead of print] DOI:https://doi.org/10.1053/j.jvca.2020.05.020
35. Ibañez C, Perdomo J, Calvo A, Ferrando C, Reverter JC, Tassies D. et al. High D dimers and low global fibrinolysis coexist in COVID-19 patients: what is going on in there?. J. Thromb. Thrombolysis 15 July 2020:1-5. <https://doi.org/10.1007/s11239-020-02226-0>
36. Nougier C, Benoit R, Simon M, Desmurs-Clavel H, Marcotte G, Argaud L. et al. Hypofibrinolytic state and high thrombin generation may play a major role in SARS-CoV2 associated thrombosis. J. Thromb. Hemost., 2020;00:1-5. Doi:10.1111/JTH.15016
37. Chaudhary R, Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Personalizing antithrombotic therapy in COVID-19: role of thromboelastography and thromboelastometry. Thromb. Haemost. Published on line 2020-07-17:1-3. <https://doi.org/10.1055/s-0040-1714217>
38. Corrêa TD, Cordioli RL, Guerra JCC, Silva BC, Rodrigues RR, Souza GM, et al. The hypercoagulability state of COVID-19 ICU patients is characterized by impaired endogenous anticoagulation and decreased fibrinolysis. Research Square July 2020:1-30. [ahead of print] DOI: <https://doi.org/10.21203/rs.3.rs-47465/v1>
39. Collett LW, Gluck S, Strickland RM, Reddi BJ,. Evaluation of coagulation status using viscoelastic testing in intensive care patients with coronavirus disease 2019 (COVID-19): An observational point prevalence cohort study. Australian Critical Care 2020 July 21:1-5. [ahead of print]. Doi: <https://doi.org/10.1016/j.aucc.2020.07.003>
40. Maatman T, Jalali F, Feizpour C, Douglas A, McGuire SP, Kinnaman G. et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe Coronavirus Disease 2019. Crit. Care Med., 2020; 48(9):e783-e790. DOI: 10.1097/CCM.0000000000004466
41. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S. et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J. Am. Coll. Surg. 2020 May 08: 193-203.e1. <https://doi,org/10.1016/j.jamcollsurg.2020.05.007>
42. Mortus JR, Manek SE, Brubaker LS, Loor M, Cruz MA, Trautner BW, et al. Thromboelastographic results and hypercoagulability syndrome in patients with coronavirus disease 2019 who are critically ill, JAMA Network Open June 2020;3(06):e2011192. doi:10.1001/jamanetworkopen.2020.11192
43. Ferrante EA, Blasier KR, Givens TB, Lloyd CA, Fischer TJ, Viola F. A Novel device for the Evaluation of Hemostatic Function in Critical care Settings. Anesth. Analg. 2016 Dec; 123(6):1372-1370. Doi:10.1213/ANAE.0000000000001413
44. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M. et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J. Thromb. Haemost. 2020;18:1747-1751. doi: 10.1111/jth.14854
45. Masi P, Hékimian G, Lejeune M, Chommeloux J, Desnos C, Chambrun MP, et al. Systemic Inflammatory response syndrome is a major contributor to COVID-19 associated coagulopathy: insights from a prospective single-center cohost study. Circulation 2020 June 23:1-8. DOI:10.1161/CIRCULATIONHA.120.048925
46. Gorlinger Klaus. Hemostasis management in thrombosis, sepsis, COVID-19 associated coagulopathy and ECMO. Oral communication April 2020, DOI:10.13140/RG.2.2.23359.46248
47. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. et al; Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, Journal Thromb. Haemost. , 2020;18(5):1094-1099. <https://doi.org/10.1111/jth.14817>
48. Thachil T, Tang N, Ganda S, Falanga A, Cattaneo M, Levi M. et al. ISTH interim guidance on recognition and management of coagulopathy in COVID‐19. J. Thromb. Haemost., 2020 ;18 :1023-1026. https://doi.org/10.1111/jth.14810
49. Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: Systematic review of reported risks and current guidelines. Swiss Medical Weekly 2020; 150:W20301:1-9. Doi:10.4414/smw.2020.20301
50. Gandhi A, Gorlinger K. Coagulopathy in COVID-19: connecting the Dots together. J. Card. Crit. Care TSS, 2020; 4:47-50. DOI:https://doi.org/10.1055/s-0040-1712739